Transcriptional Analysis of Pluripotency Reveals the Hippo Pathway as a Barrier to Reprogramming.

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Public Summary:
Induced pluripotent stem cells can be generated from adult skin cells hold enormous promise for new therapies for degenerative diseases. However, skin cells are expected to have active genes that antagonize the induction of pluripotency, thereby making this process very inefficient. In this article we identify a novel set of genes that act as a barrier to induction of pluripotency, we described how they work in this context. We further find that a key barrier gene, LATS2, is repressed during testicular cancer, suggesting that induction of pluripotency may have genetic parallels to this type of cancer.

Scientific Abstract:
Pluripotent stem cells are derived from culture of early embryos or the germline, and can be induced by reprogramming of somatic cells. Barriers to reprogramming are expected to exist that stabilize the differentiated state and have tumor suppression functions. However, we have a limited understanding of what such barriers might be. To find novel barriers to reprogramming to pluripotency, we compared the transcriptional profiles of the mouse germline to pluripotent and somatic cells, in vivo and in vitro. There is a remarkable global expression of the transcriptional program for pluripotency in Primordial Germ Cells (PGCs). We identify parallels between PGCs reprogramming to pluripotency and human germ cell tumorigenesis, including the loss of LATS2, a tumor suppressor kinase of the Hippo pathway. We show that knockdown of LATS2 increases the efficiency of induction of pluripotency in human cells. LATS2 RNAi, unlike p53 RNAi, specifically enhances the generation of fully reprogrammed iPS cells without accelerating cell proliferation. We further show that LATS2 represses reprogramming in human cells by post-transcriptionally antagonizing TAZ but not YAP, two downstream effectors of the Hippo pathway. These results reveal transcriptional parallels between germ cell transformation and the generation of iPS cells, and indicate that the Hippo pathway constitutes a barrier to cellular reprogramming.